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Chemoselective and Solvent-Free Thioacetalization of Aldehydes by a Catalytic Amount of NBS

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Abstract: A chemoselective, straightforward, and rapid method for thioacetalization of aldehydes by use of 1,2-ethandithiol and a catalytic amount of *N*-bromosuccinimide under solvent-free conditions is reported. The reaction takes place in excellent yields and short reaction times.

Keywords: Thioacetalization, NBS, solvent-free, chemoselective, aldehydes

INTRODUCTION

One of the major challenging problems during multistep syntheses is protection of carbonyl functional groups from nucleophilic attack until their electrophilic nature is exploited. For this reason, the protection of carbonyl groups is essential for organic chemists. Among carbonyl protecting groups, dithioacetals constitute an important class of compounds as acyl anion equivalents[1] or masked methylene functions in carbon–carbon bond-forming reactions. On the other hand, these substrates are versatile[2] because of their straightforward preparation and also their stability under basic or mildly acidic conditions.[3,4]

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Generally, thioacetals are prepared by condensation of carbonyl compounds with thiols or dithiols employing strong acid catalysts such as HCl,[5] PTSA,[6] $AlCl_3$,[7] $TiCl_4$,[8] and $LaCl_3$.[9] A large number of these methods require long reaction times, reflux temperature, and stoichiometric amounts of catalyst and provide low yields. Most recently, some methods employing LiBr,[10] $LiBF_4$,[11] $InCl_3$,[12] $Sc(OTf)_3$,[13] and I_2[14] have been reported. Interestingly, only a few of these methods have demonstrated chemoselective protection of aldehydes in the presence of ketones. Some methods failed to protect deactivated aromatic substrates.[13] Therefore, there is still a need to develop a simple and efficient method for chemoselective protection of aldehydes.

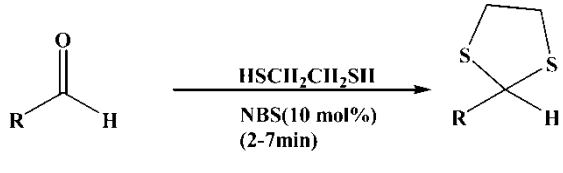
RESULTS AND DISCUSSION

In continuation of our research on ammonium and phosphonium salts,[15] in this communication we introduce a mild and highly chemoselective procedure for thioacetalization of aldehydes in the presence of ketones using 1,2-ethandithiol in the presence of a catalytic amount of *N*-bromosuccinimide under solvent-free conditions (Scheme 1).

In comparison to the reported[16] method for thioacetalization of aldehydes using NBS as catalyst, which suffered from using an organic solvent such as dichloromethane and longer reaction times (30–180 min), in our method the reaction was carried out under solvent-free conditions with higher yields and the reaction time is much more shorter (2–7 min) (Table 1).

Moreover, this procedure is highly chemoselective, providing selective protection of an aldehyde in the presence of a ketone. Treatment of an equimolar mixture of benzaldehyde and acetophenone in the presence of 1,2-ethanedithiol and a catalytic amount of NBS under solvent-free conditions produced only 1,3-ditholane derivative of the benzaldehyde, whereas the acetophenone was completely was recovered. This competitive reaction illustrating the chemoselectivity of the present method (Scheme 2).

In conclusion, we have developed a simple and efficient method for chemoselective dithioacetalization of various aldehydes under solvent-free conditions with high yields and short reaction times. This method is a chemoselective procedure for protection of aldehydes in the presence of ketones.



1 2

R = Alkyl, Aryl

Scheme 1.

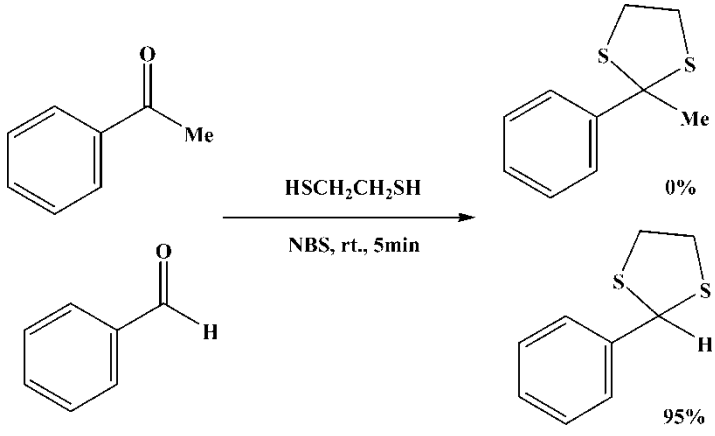
Table 1. Thioacetalization of aldehyde with NBS under solvent-free conditions at room temperature[a]

Entry	R_1	Time (min) [sol][c]	Yield (%)[b] [sol][c]
1a	Ph	5 [40]	97 [80]
1b	2-(Cl)C_6H_4	7	95
1c	3-(Cl)C_6H_4	3	98
1d	4-(Cl)C_6H_4	2 [30]	95 [80]
1e	3-(O_2N)C_6H_4	5	95
1f	4-(O_2N)C_6H_4	5	90
1g	2-(MeO)C_6H_4	7	95
1h	3-(MeO)C_6H_4	3	98
1i	4-(MeO)C_6H_4	5 [30]	96 [75]
1j	4-(Me)C_6H_4	2	98
1k	2-(HO)C_6H_4	7	95
1l	5-(Br)-2-(HO)C_6H_3	5	98
1m	4-(Br)C_6H_4	3	95
1n	3,4-(Dimethoxy)C_6H_3	3	98
1o	2,4-(Dimethoxy)C_6H_3	5	95
1p	4-(Me_2N)C_6H_4	3	98
1q	2-Furyl	3 [30]	92 [90]
1r	2-(5-(Me)Furyl)	3	98
1s	PhCH═CH	5	95

[a]Confirmed by comparison with authentic samples (TLC, IR, and NMR).

[b]Yield of isolated pure product after purification.

[c]Reaction in dichloromethane solution.[15]



Scheme 2.

EXPERIMENTAL

General

Yields refer to isolated pure products. The products were characterized by comparison of their spectral (^{1}H NMR, IR), melting point, and boiling point with authentic samples (authentic samples prepared by reported methods).[17] All ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$, relative to TMS (0.00 ppm). All reactions were carried out under solvent-free conditions at room temperature in a hood with strong ventilation.

Dithioacetalization of 4-Methylbenzaldehyde 1j: A Typical Procedure

A mixture of 4-methylbenzaldehyde **1j** (10 mmol, 1.20 g), 1,2-ethanedithiol (12 mmol, 1.13 g), and NBS (1 mmol, 0.18 g) in a mortar was ground with a pestle for the time specified in Table 1. Monitoring the reaction by TLC (silica-gel ethyl acetate–cyclohexane, 15:85). After disappearance of the starting material, the mixture was washed with Et_2O (4×10 mL) and filtered. The filtrated was evaporated under reduced pressure. Evaporation of the solvent gave 2-(4-methylphenyl)-1,3-dithiolane **2j**. The yield was 1.92 g (98%) of colorless solid **2j**, mp 55–57°C. IR (neat): 3004, 1510, 1437, 1411, 1277, 1177, 1165, 830, 777 cm^{-1}. ^{1}H NMR: δ 2.32 (s, 3 H), 3.29–3.52 (m, 4 H), 5.62 (s, 1 H), 7.10 (d, $J = 6.5$ Hz, 2 H), 7.40 (d, $J = 6.5$ Hz, 2 H). ^{13}C NMR: δ 21.11, 40.20 (2 CH_2), 56.12, 127.80, 129.15, 137.10, 137.84.

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